LETTERS

Botulinum toxin type B in blepharospasm and hemifacial spasm

Botulinum neurotoxins (BTXs) inhibit the presynaptic release of acetylcoline causing a chemical denervation that results in sustained muscle weakness and have been used in the past 20 years to induce selective blocking of hyperactive striatal (and smooth) muscles.[1] All the different seven serotypes of BTXs have in common the mechanism of action (block of the neuroexocytosis machinery inside the end plate, responsible for the release of acetylcholine into the neuromuscular junction), acting on different targets. The two commercially available serotypes, botulinum toxin type A and botulinum toxin type B (abbreviated BTX-A and BTX-B, respectively) are reported to act as zinc dependent endopeptidases on different intraneuronal target proteins.

The clinical value of BTX-A has been recognised for a long time and is widely demonstrated by hundreds of clinical reports. More recently a clinical usefulness of BTX-B has been investigated. Two controlled clinical trials have demonstrated that local intramuscular injections of BTX-B are effective in the treatment of cervical dystonia in patients with BTX-A responsive disease,[2] as well as in patients with BTX-A resistant disease (secondary non-responders).[3] BTX-B was found to be effective in both studies, with a significant improvement observed in all the parameters investigated (severity, disability, and pain); action was found to last as long as 16 weeks.[2 3]

Based on these favourable results, we investigated BTX-B treatment in blepharospasm (BLS), another common form of focal dystonia, and in hemifacial spasm (HFS). Indeed, despite BTX-A being an efficacious treatment for these conditions,[4] a percentage of patients still shows a suboptimal response, particularly in long term treatments. They could, therefore, benefit from the availability of another botulinum toxin serotype.

Blepharospasm

We studied 13 subjects (10 women and 3 men; mean (SD) age at onset 51.5 (15.0) years; mean disease duration 9.1 (8.1) years) with BLS. BLS was diagnosed as idiopathic focal dystonia in 12 patients, and as tardive dystonia in one case. All patients had received BTX-A before, with a moderate to good response. Patients were excluded if they had received a BTX-A injection in the past three months for their BLS. After an informed consent was obtained, four pretarsal injections were placed around each eye; the fixed total dose for each treatment was 2500 units (0.8 ml of a solution obtained by adding 0.3 ml of saline to 0.5 ml of the commercially available BTX-B solution). Before each treatment, patients were assessed with an objective rating scale for dystonia (Burke-Fahn-Marsden scale, severity factors, items for BLS[5]); efficacy was assessed at the time of the peak effect (7–14 days after treatment) with the same rating scale and with a visual analogue scale assessment (Patient Global Assessment of Change), in which improvement was subjectively measured from 0% to 100%. Latency of the effect was defined as the time between the treatment and the first detectable clinical effect. Duration of effect was defined as the time between the first detectable clinical effect and the moment when that any benefit has completely worn off, both as reported by the patient. Each patient received a single treatment. Additionally, a telephone call was made to the patient each week to assess safety and duration of the effect.

Results of the trial are reported in table 1. Overall five patients rated the efficacy of BTX-B as superior to BTX-A and preferred to continue treatment with BTX-B. The drug was generally well tolerated, with the most common adverse effect of BTX-B being pain during the injection, which was reported by 11 of 13 of the patients. Other common side effects of BTX-A treatment, such as ptosis and epiphora, were mild and transient. One patient experienced an anaphylactic reaction, consisting of Quincke's oedema, from day two after the injection, though this resolved after treatment with corticosteroids.

Table 1 Response to BTX-B injections

	BLS		HFS	
	Before	After	Before	After
Latency to response (days)		3.0 (2.5)		3.7 (6.01)
Duration of response (days)		63.0 (17.5)		46.5 (22.1)
Objective rating scale (points)	1.9 (0.4)	1.1 (0.6)*	1.9 (0.8)	0.5 (0.5)*
Subjective visual analogue scale (%)		35.1 (28.5)		59.8 (26.9)

Results are expressed as mean (SD). *Student's *t* test between before and after injection: p<0.001.

Hemifacial spasm

We studied 11 subjects (six men and five women; mean age at onset 64.9 (10.4) years; mean disease duration 5.4 (3.9) years) with primary HFS. All patients had received BTX-A before, with a moderate to good response. Patients were excluded if they had received a BTX-A injection in the past three months for their HFS. After an informed consent was obtained, four pretarsal injections were placed around each eye, and two around the mouth; the fixed total dose of BTX-B for each treatment was 937.5 units. This was obtained taking 0.3 ml of the previously described solution. Before each treatment, patients were assessed with an objective rating scale for dystonia (Burke-Fahn-Marsden scale, severity factors, items for BLS and mouth averaged[5]; this scale was used in the absence of validated rating scales for HFS); efficacy was assessed at the time of the peak effect with the same objective rating scale and the subjective visual analogue scale reported above. Each patient received a single treatment. Latency and duration of the effect were assessed as above.

Results of the trial are reported in table 1. Only two patients rated the efficacy of BTX-B as superior to BTX-A and preferred to continue treatment with BTX-B. The drug was well tolerated, with the most common adverse effect being burning pain during the injection, which was reported by 7 of 11 patients. Other common side effects of BTX-A treatment were negligible.

Comment

This open pilot trial, which is the first to use BTX-B in a neurological condition other than cervical dystonia, suggests that BTX-B is an effective and safe treatment for both BLS and HFS. The time course and magnitude of the improvement observed in our study are similar to those reported in trials with BTX-A for the same conditions, while the duration of the effect appears shorter as the mean duration of effect with BTX-A in these neurological conditions is 12–16 weeks.[4] The only peculiar side effect was local pain during the injection, which has not been reported before in trials with BTX-B. This event might to be related to the fact that BTX-B is available in a liquid preparation, which has different biochemical properties than the reconstituted solution of BTX-A.[2–4] The severe, adverse reaction reported in a single patient with BLS has not been described in previous trials using this compound for cervical dystonia and has rarely been reported in conjunction with BTX-A use[6]; it should, however, not discourage the planning of further dose ranging studies of BTX-B and studies on larger series of patients designed to compare the effect of BTX-B with both placebo and BTX-A in different neurological disorders.

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C Colosimo, M Chianese, M Giovannelli
Dipartimento di Scienze Neurologiche, Università La Sapienza, Rome, Italy

M F Contarino, A R Bentivoglio
Istituto di Neurologia, Università Cattolica del S Cuore, Rome, Italy

Correspondence to: Dr C Colosimo, Dipartimento di Scienze Neurologiche, Università La Sapienza, viale dell'Università 30, I-00185 Rome, Italy; carlo.colosimo@uniroma1.it

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Persistent bitter taste as an initial symptom of amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is characterised by progressive degeneration of upper and lower motor neurones. Clinical symptoms involve weakness, dysphagia, dysarthria,

muscle atrophy and fasciculations, hyperreflexia, spasticity, Babinski signs, and clonus. Here we report on two patients with sporadic ALS in whom the disease initially presented with a persistent bitter "metallic" taste.

Case reports

Patient 1 was a previously healthy 60 year old women. Six months before admission, she noticed a persistent bitter taste, dysarthria, and emotional liability. Several weeks later she noticed a progressive weakness in both legs which spread to both arms within four months. At the time of admission, she had bilateral bulbar weakness, episodes of pathological crying, generalised spasticity, muscle atrophy, weakness, and fasciculations. The plantar reflex was extensor on the left side. The remaining neurological examination was unremarkable.

Patient 2 was a previously healthy 64 year old women. At the time of admission, she reported a four month history of a persistent bitter "metallic" taste confined to the posterior tongue, facial weakness, and clumsiness of the left hand. Neurological examination revealed bilateral bulbar weakness, an increased jaw reflex, slow side to side tongue movement, generalised hyperreflexia, and fasciculations. Spasticity, muscle atrophy, and weakness were predominantly observed in the left arm. The remaining neurological examination was normal.

The patients had not taken prescription or non-prescription drugs during the months preceding the symptoms, or at the initiation of symptoms or at the time of admission. Oral hygiene was good in both cases and xerostomia was not evident. Family history was negative. The occupational and chemical exposure history was unremarkable.

Spatial gustatory function testing with sodium chloride (0.04 and 0.32 M), sucrose (0.07 and 0.32 M), citric acid (0.01 and 0.02 M), and quinine (0.00016 mM) was undertaken. Although both patients described the perception of a bitter taste throughout the examination, the test did not reveal hypogeusia for any quality. In both cases, routine blood chemistry and cerebrospinal fluid studies were normal. Tests for paraneoplastic autoantibodies (Hu, Yo, Ri, Ma, Ta, CV2) were negative. Cranial and spinal magnetic resonance imaging showed mild bilateral atrophy of the precentral gyrus in both patients. Motor evoked potentials revealed slowed central conduction. Peripheral electrophysiological testing showed active denervation, normal nerve conduction, and normal F wave latencies. Thus motor neuropathy with multifocal conduction block, cervical myelopathy, and paraneoplastic motor neurone disease could be excluded. A diagnosis of clinically definite ALS was made, based on the revised El Escorial criteria (http://www.wfnals.org/articles/elescorial1998.htm). Treatment with riluzole and α tocopherol was initiated in both patients.

Comment

To our knowledge, dysgeusia has not been described in this disease. The persistent perception of bitter taste developed as an early symptom of the disease in our patients. In this regard, it resembles the dysgeusia known from ciguatera food poisoning, which is thought to produce a bitter taste by blocking sodium channels.[1] However, other sensory symptoms were absent, both clinically and electrophysiologically. The chorda tympani branch of the facial nerve carries taste sensations from the anterior two thirds of the tongue, whereas the glossopharyngeal nerve and the vagus nerve innervate the posterior third and the epiglottis. It has been shown experimentally and clinically that anaesthesia of the chorda tympani nerve branch results in intensified perception of bitter taste from the posterior tongue, suggesting that input by way of the chorda tympani normally inhibits the glossopharyngeal and vagus nerve input.[2] In fact, spontaneous bitter taste dysgeusia (phantogeusia) similar to that perceived by our patients was observed in the posterior tongue after anaesthesia of the chorda tympani.[2] Hence it may be speculated that mild sensory neuropathy of the chorda tympani branches may be responsible for our findings. Sensory signs have indeed been described in ALS. However, if at all, they develop relatively late in the disease.[3] Furthermore, the spatial gustatory function test did not reveal hypogeusia confined to a localised region of the tongue in our patients, although the sensitivity of this test for mild gustatory disturbances is probably low.[4] Unfortunately, neither patient was available for electrogustometry to further clarify our hypothesis.

Alternatively, the dysgeusia may be of central nervous origin. Both patients presented with bilateral nuclear facial paresis reflecting a prominent bulbar involvement in the disease. Thus it may be speculated that bilateral degeneration of the brain stem solitary tract nucleus may be responsible for the dysgeusia in our patients. Interestingly, dysfunction of the autonomic nervous system—which in part is also regulated by the solitary tract nucleus—has been described in ALS,[5] supporting the view that this disease may be a multisystem disorder. Thus dysgeusia may indicate brain stem involvement in the disease. As a bulbar onset of ALS is an important predictor of the disease course,[6] our finding may also be of prognostic value. We cannot provide a definite neuroanatomical basis for our observation, but we believe that future studies may be able to address these issues.

G C Petzold, K M Einhäupl, J M Valdueza
Department of Neurology, Charité Hospital, Humboldt University, Schumannstr 20/21, 10098 Berlin, Germany

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Correspondence to: Dr Petzold; gabor.petzold@charite.de

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Schizophrenia and episodic ataxia type 2

The frequent co-occurrence of degenerative cerebellar pathology and schizophrenia, as well as the recently reported increased association rate between autosomal dominant ataxias and major psychosis, strongly suggests the involvement of the cerebellum in the pathophysiology of schizophrenia.[1–3] The analysis of associations between psychosis and neurodegenerative diseases may improve our understanding of the pathophysiology of schizophrenia and facilitate the search for susceptibility genes for this disorder.[4]

To our best knowledge, there have been no previous reports about an association between schizophrenia and the periodic autosomal dominant ataxias, such as episodic ataxia type 1 and type 2 (EA1 and EA2). We present a case of a young man who has been diagnosed with paranoid schizophrenia (ICD-10: F20.0) and episodic ataxia type 2.

Case study

The patient, a man aged 27 years, was first admitted to our hospital with psychotic symptoms in June 1995. He presented with paranoid delusions and delusions of reference, acoustic hallucinations (commenting voices), formal thought disorder, and behaviour disorganisation, as well as negative symptoms such as blunted affect, poor rapport, and lack of spontaneity. At this time, he was diagnosed as having paranoid schizophrenia (ICD-10: F20.0) and showed a PANSS (positive and negative symptom scale) total score of 137 (fig 1).

The patient was initially treated with risperidone (6 mg/d) which led to a slight improvement in his psychotic symptoms. After discharge from our hospital in September 1995 he regularly attended our outpatient clinic. Despite treatment with risperidone and later with haloperidol decanoate (20 mg/2 weeks), he continued to have chronic psychotic symptoms, which persisted until readmission in April 2001. At this admission he was suffering from severe psychosis (paranoid delusions, acoustic hallucinations, formal thought disorder, and behaviour disorganisation) and negative symptoms (fig 1). Antipsychotic treatment with quetiapine (800 mg/d; 4 weeks) and subsequently with amisulpride (600 mg/d; 4 weeks) did not lead to any improvement in the psychosis. At this time, a neurological investigation showed gaze evoked nystagmus and upward gaze palsy, though attacks of ataxia had neither been reported by the patient nor noticed by the nurses.

Because of persistence of the psychotic symptoms, we began treatment with clozapine (400 mg/d) and observed a gradual deterioration in psychosis over the next four weeks despite sufficient serum levels of clozapine. At that time the first severe ataxia attacks appeared. They were manifested by gait ataxia, dysarthria, and slight intention tremor of the upper extremities and persisted for at least several hours. After other causes of cerebellar dysfunction—such as inflammatory, toxic, and vascular disorders—had been excluded, the patient was diagnosed as having episodic ataxia type 2 because he met the following clinical diagnostic criteria: duration of episodes (hours to days), gait and stance ataxia, interictal absence of most symptoms (except oculomotor deficits). Consequently, we began treatment with acetazolamide (200 mg twice daily) and switched the antipsychotic medication from clozapine to zotepine (400 mg/d). This led to both a complete elimination of ataxia episodes and a gradual amelioration of the psychotic symptoms. At the time of discharge six weeks later, the patient's total PANSS score was 90. At all subsequent follow up investigations undertaken monthly until December 2002 the psychiatric symptoms remained unchanged (fig 1) and there was no recurrence of the ataxia attacks.